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# A THEORY OF THE NATURE OF PROTOPLASMIC RESPIRATION AND GROWTH.

A. P. MATHEWS.

Respiration is probably the most fundamental of living processes. It is common to all forms of protoplasm ; as long as it persists, protoplasm is said to live ; when it ceases protoplasm dies ; and it is the point of attack of the most powerful poisons such as the isocyanides. Most of the other protoplasmic functions depend directly or indirectly on respiration as, for example, the discharge of impulses from the nerve cells, the beating of the heart and so on. The protoplasmic syntheses and many of the decompositions have been ascribed since Drechsel's work and that of Hoppe-Seyler to this fundamental process.

In any general theory of respiration the following facts have to be explained :

1. Even though surrounded by oxygen all protoplasm maintains itself while alive in a reduced state and acts as an intense reducing agent. Its reducing powers are comparable to those of nascent hydrogen.

2. For all forms of protoplasm free oxygen above a certain tension is an intense poison. For some forms this tension may be no more than a very small fraction of an atmosphere ; for others it is from three to four atmospheres.

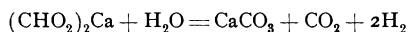
3. Atmospheric oxygen has little oxidizing power ; whereas protoplasm brings about oxidation of the most radical nature and is comparable in its oxidizing powers to the most intense chemical oxidizing agents.

4. Hydrogen is evolved as a gas by a great variety of bacteria and moulds.

5. The production of carbon dioxide by protoplasm stands in no direct or immediate relation to the consumption of free oxygen.

6. Many forms of protoplasm such as the anærobic bacteria are able to bring about intense oxidations in the absence of atmospheric oxygen.

The only general theory of the nature of respiration which has been carefully worked out is that of Hoppe-Seyler.<sup>1</sup> According to this hypothesis there occurs in the cell a fermentative decomposition of some substance analogous in all respects to the fermentative decomposition of calcium formate by many bacteria.



By this fermentation nascent hydrogen is set free; the nascent hydrogen keeps the protoplasm in its reduced state; it combines with one atom of the oxygen of the air to form water and sets free the other atom as nascent oxygen which thus causes the intense oxidations of protoplasm. This hypothesis was attacked by Traube, who showed in many cases that the process included the formation of hydrogen peroxide which was the real oxidizing agent. Hoppe-Seyler demonstrated, however, that some of these oxidations were more powerful than hydrogen peroxide, which is not a very strong oxidizing agent, could produce.

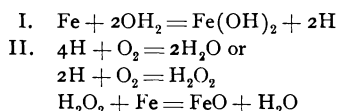
With the discovery of the oxidases, Hoppe-Seyler's hypothesis has fallen into the background without the oxidase hypothesis giving a better explanation in its stead. The manner of action of the oxidases is still obscure; their chemical composition is unknown, and no oxidase will cause oxidations in the absence of oxygen, whereas many forms of protoplasm can carry out such oxidations in the presence of no free oxygen at all or only of traces of free oxygen.

The studies of Armstrong, Dixon and others on the processes of slow and explosive oxidations and combustions throw, in my opinion, a remarkably clear light on protoplasmic respiration. These authors have shown that in ordinary oxidation the presence of some water is necessary to the oxidation. Phosphorus in a perfectly dry state will not ignite in dry air. Armstrong<sup>2</sup> concludes that the primary oxidation in all these cases is not brought about by the gaseous oxygen, but by the water. The atmospheric oxygen acts the part only of a depolarizer to take care of the nascent hydrogen formed from the water.

<sup>1</sup> Hoppe-Seyler, *Physiologische Chemie*, I. Theil, Allgemeine Biologie, p. 126 ff. Berlin, 1877.

<sup>2</sup> Armstrong, *Chemical News*, July 15, 1904, vol. 90, p. 25; *Transactions Chemical Soc.*, vol. 63, p. 1088, 1903.

The formula for the rusting of iron on this hypothesis would be as follows :

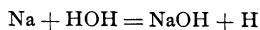


Reaction I. cannot go on unless oxygen is present to remove the nascent hydrogen. If no oxygen is present the nascent hydrogen at once reduces the iron oxide and forms metallic iron again. The atmospheric oxygen does not unite with the iron, but with the hydrogen.

The same hypothesis will explain protoplasmic respiration and at once makes clear the identity of anærobic and ærobic respiration. The following theory of respiration is founded in part on Armstrong's work.

The real respiration of all forms of protoplasm, both ærobic and anærobic, is brought about not by the oxygen of the air, but by that of the water. The hydrogen set free from the water combines with other elements of the protoplasm, thus keeping it reduced; it also combines with the oxygen of the air if this is present to form water; and in the absence of oxygen it may escape as free hydrogen.

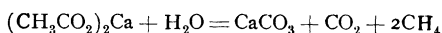
The only difference between anærobic and ærobic respiration is that the anærobic protoplasm is so powerful a reducing agent that it is able to drive hydrogen out of the water, thus oxidizing itself without the aid of atmospheric oxygen to act as a depolarizer. Ærobic protoplasm being less powerfully reducing requires the presence of more or less oxygen to take care of the hydrogen. The difference between these different kinds of protoplasm is exactly the difference between metallic sodium and metallic iron. Sodium is so powerful a reducing agent that it oxidizes itself at the expense of water driving out hydrogen even in an atmosphere of hydrogen. This corresponds to anærobic protoplasm :



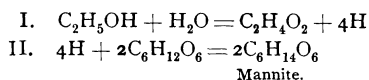
Iron is so weak a reducing agent that it requires the presence of free oxygen to take care of the hydrogen set free, before it will oxidize itself. This corresponds to ærobic respiration. Pro-

toplasmic respiration, therefore, is in reality not the consumption of gaseous oxygen and the liberation of carbon dioxide as ordinarily stated. We now know that the production of carbon dioxide stands in no direct causal relation to the consumption of oxygen. *Respiration is in fact the dissociation of water with the liberation of hydrogen.*

The evidences of the truth of this hypothesis are many and have been collected in part by Hoppe-Seyler. Hydrogen is produced and set free as such by a great many moulds and bacteria, *i. e.*, *coli communis*, *penicillium*, *butyricus*, etc. In the case of facultative anærobes like the colon bacillus, the hydrogen appears only if no atmospheric oxygen is present; it is burned to water if this be present. In many cases where the hydrogen is not set free as such it escapes as marsh gas or combines with the protoplasm or some of the constituents of the culture medium, such as levulose or sulphur. Thus as Hoppe-Seyler showed, in the fermentation of calcium acetate the hydrogen unites with the methyl or methylene set free by fermentation and comes off as marsh gas.



In the second place hydrogen is set free in the case of some bacteria which are able to oxidize substances in the absence of oxygen. In this case the oxygen can only have come from the water. Such a case has been reported recently by Mazé.<sup>1</sup> In the case of a certain bacterium alcohol was oxidized to acetic acid in the absence of air, if levulose was present. The levulose was at the same time converted into mannite. The reaction was probably as follows:



Reaction I. can only go on in a positive direction or from left to right if some substance is present to remove the hydrogen and thus prevent equilibrium from being established.

It will be seen that as atmospheric oxygen acts the part only of a depolarizer any other oxidizing agent, that is any other sub-

<sup>1</sup> Mazé, *Annales de l'Institut Pasteur*, XVII.

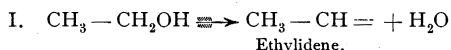
stance which unites readily with nascent hydrogen can replace the atmospheric oxygen and permit oxidation to go on in the absence of air. In the example just cited levulose acts in this way. This principle is of considerable importance in bacteriology.

The hypothesis just stated necessitates, as will be seen, a total abandonment of the common interpretation of anærobic respiration as taking place at the expense of the oxygen of some food stuffs and shows at a glance the identity of the process in ærobic and anærobic forms.

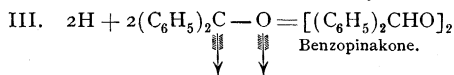
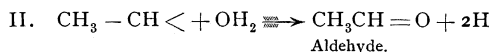
What is the nature of the process going on in protoplasm by which this decomposition of water is produced?

A great number of reactions occur of just this type in organic and inorganic chemistry. One of the most striking is the oxidation of alcohol to aldehyde accompanied by the reduction of benzophenone to benzopinakon which occurs when an alcoholic solution of benzophenone is exposed to sunlight. The interpretation of this reaction as given by Nef's<sup>1</sup> brilliant hypothesis gives at the same time an interpretation of the living respiration which wonderfully simplifies the problem of the chemical basis of life.

According to Nef many organic reactions are brought about by a change in valence of the carbon atom from four to two. In the case just cited alcohol in the sunlight splits off water to some degree just as it does when heated and forms extremely active ethylidene particles as follows :



If now benzophenone is present to act as a depolarizer the active ethylidene attacks the water and oxidizes itself to aldehyde setting free nascent hydrogen which reduces the benzophenone.

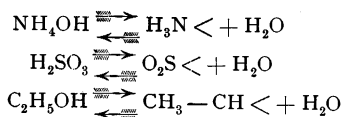


It will be seen how exactly this process fulfills the requirements of the facts for a complete theory of respiration. Owing,

<sup>1</sup> Nef, *Liebig's Annalen*, vol. 335, 1904, p. 192.

therefore, to Nef's hypothesis, and without this the exact mechanism of the process would be obscure, the following picture of protoplasmic respiration may be formed :

In protoplasm there is some substance (or substances) of unknown nature which splits off water from itself just as the alcohol does in the above reaction or as ammonium hydrate does and sets free from itself active particles having the properties of ethylidene. The following three well known reactions are exactly similar to this primary process :

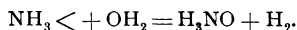


For protoplasm the reaction is as follows :



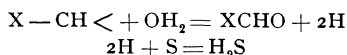
In this reaction  $\text{R}-\text{CH}_2\text{OH}$  is some unknown substance.

The nature of the substances thus reacting in protoplasm is unknown. There is no evidence, however, nor is there any reason for assuming that they are complex substances. It is probably not a substance acting by means of a change in valence of nitrogen for the reason that the nitrogen substances such as ammonia do not have so great an affinity for oxygen as that required of the unknown substance. We do not get for example such a decomposition of ammonia as this :

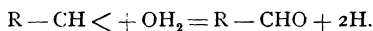


On the other hand the substance possesses the powers ascribed by Nef to bivalent carbon. Carbon has a powerful affinity for oxygen. It may well be, therefore, that the substance is a carbon compound, presumably of simple nature and derived directly or indirectly from the foods so that new raw material for the reaction is constantly supplied. If this is the case Nef's view that bivalent carbon is at the bottom of the vital reaction would be justified.<sup>1</sup>

<sup>1</sup> Probably all reducing agents act in some measure in this way. For example in egg white a substance is present which forms sulphuretted hydrogen in the presence of sulphur. This substance is of unknown nature. The reaction probably is a follows :



Whatever their composition may be the active particles attack the water of the protoplasm, oxidize themselves to aldehydes and set free nascent hydrogen.



This explains the presence of aldehydes in protoplasm; the production of hydrogen by many or all forms of protoplasm as assumed by Hoppe-Seyler and the keeping of the cell protoplasm in a reduced state. It is perfectly clear that surrounded by oxygen as most protoplasm is it could not possibly continue in its reduced condition if some strong reducing agent such as hydrogen was not constantly produced. If too much free oxygen is present the aldehydes will be converted into acids, the reaction of the protoplasm changed and the life of the cell destroyed. Oxygen in other words above a certain pressure is poisonous for protoplasm.

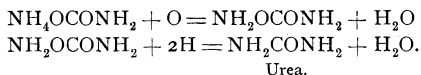
In those forms of protoplasm called anærobic the active particles are of such a character and so powerful that in the absence of oxygen they can like sodium, oxidize themselves and set free hydrogen; or in the presence of certain foods which will combine with hydrogen such as levulose, they are able to oxidize themselves. In those forms of protoplasm called ærobic the active particles are not so powerful and require the aid of atmospheric oxygen to combine with the hydrogen before they can decompose water. While the active particles are formed spontaneously, the conditions in protoplasm may be such as to accelerate their formation (ferment action, see Nef).

A few examples will perhaps make clear the possible relations of this fundamental reaction to the synthetic properties of the protoplasm. The fundamental nature of most of these syntheses is simple and consists in the elimination of water between two simple molecules to form a complex molecule, as for example, in the condensation of the amino acids to form albumin; of the monosaccharids to form disaccharids and polysaccharids; of the amino acids to form pyrimidin; of the alcohols and fatty acids to form fats; of ammonia and oxyacids to form amino acids.

Two explanations of this process may be given. That of Drechsel is the first. According to this theory the elements to

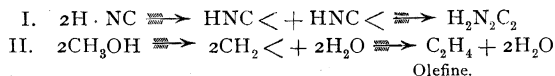


form water are eliminated by a successive oxidation and reduction of the substances. A type of this reaction is the conversion of ammonium carbamate into urea.



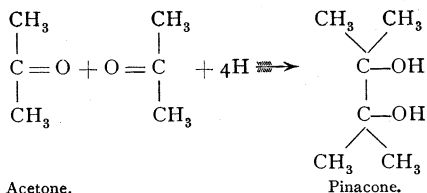
Upon the basis of this hypothesis, Drechsel succeeded outside the cell by rapidly alternating reductions and oxidations produced by induction shocks in obtaining urea from albumin; in synthesizing hippuric acid from benzoic acid and glycocholl, and in synthesizing ethereal sulphates. These syntheses may thus very readily be the secondary result of that fundamental respiratory process characterized as it is by a simultaneous reduction and oxidation.

The syntheses may also be due as shown by Nef for many reactions to the condensation of active particles, that is particles formed by the dissociation of organic substances and containing open valencies. A typical synthesis of this sort would be the formation of olefine gas from methyl alcohol, or the condensation of the isocyanides.



If in protoplasm conditions are such as to cause a good many active particles to be produced, syntheses by condensations of all kinds must spontaneously and of necessity occur. In this way it is seen that both growth and respiration are due to the spontaneous formation of active particles from the foods.

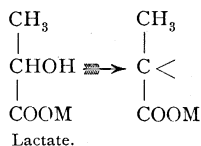
In the third place, mere reduction may cause many syntheses. A typical example of this sort is the condensation of acetone by nascent hydrogen.



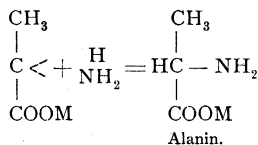
In this case a forked chain is produced, in which the carbon atoms are attached directly.

Moreover, from the aldehydes produced in the way indicated, all manner of compounds will originate spontaneously, as Loew has particularly pointed out. Thus from formaldehyde, formose and the sugars spontaneously originate in faintly alkaline solutions; glycerine aldehyde goes over of itself into a hexose sugar; acetic aldehyde in the presence of ammonium cyanide forms propionic amido-nitril, which readily passes into amido propionic acid or alanin, one of the most common constituents of the albumins. The albumins themselves are nothing else, as Kossel and Fischer have shown, than condensed amino acids. This condensation, there is every reason to believe, can be brought about by cell extracts, since from the kidney a substance has been isolated which brings about identically the same kind of a condensation, namely, that of benzoic acid and glycoll, to form hippuric acid. Finally, by spontaneous union of the aldehydes with the cyanides found in so many cells, carbon chains are built up readily outside the cell and presumably in the cell also, since nitrils are not uncommon constituents of protoplasm.

Many other examples might be given here, but these will, I think, indicate how completely the formation of substances found in protoplasm can be accounted for by means of this fundamental reaction which is going on. These syntheses and decompositions must take place as a matter of course if the reaction is of the nature sketched. I do not mean to imply that the amino acids, for example originate altogether in the manner indicated. They may also be formed by the union of oxyacids dissociated in Nef's sense with  $\text{NH}_3$ , without the intermediate formation of aldehydes or ketones. Nef has shown that the lactates for example dissociate as follows :



If now  $\text{NH}_3$  is present, union takes place directly with the bivalent carbon atom.



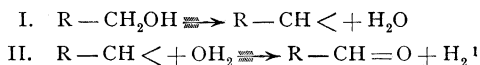
In any case it will be apparent that the synthetic powers of the cell depend on the same process as the respiratory powers.

While the interpretation of the exact mechanism by which the respiratory substance or substances (for there may be many such substances in one cell) dissociate water depends, as will be seen, upon Nef's hypothesis and is due to this hypothesis, the general hypothesis that such dissociation of water is taking place and that this is the basis of respiration, is independent of Nef's hypothesis. If, however, that hypothesis be accepted, and of its truth he has already produced so many proofs as to entitle it to provisional acceptance, we can go farther and ascribe this most fundamental of living reactions and many protoplasmic syntheses to methylene dissociation, that is, to bivalent carbon particles in protoplasm, as Nef himself has pointed out. Protoplasmic respiration must in any case be defined in the light of known facts somewhat differently from the ordinary statement.

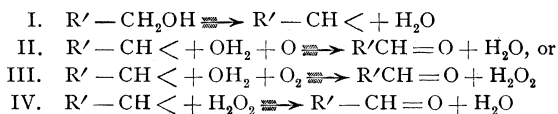
Respiration is that process going on in protoplasm by which water is decomposed into oxygen and hydrogen. The oxygen combines with the substances of the protoplasm thus oxidizing them; the hydrogen is either set free in the gaseous form, or it is united with atmospheric oxygen to form water; or it combines with other substances in the protoplasm.

The reaction may be written as follows:

For anærobic protoplasm:



For ærobic protoplasm:



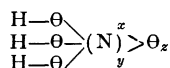
<sup>1</sup> A great number of reactions of this type are given in Nef's paper already referred to. See also Nef, *Journal of the American Chemical Society*, Vol. XXVI., 1904, p. 1549.

The views expressed in this paper may be harmonized with those in a previous paper in which the oxidations and reductions going on in protoplasm were regarded as electrical,<sup>1</sup> if the following explanation of the dissociation of  $\text{NH}_4\text{OH}$  into  $\text{NH}_3$  and  $\text{H}_2\text{O}$  be adopted. At present no clear connection between ionic dissociation and such dissociations as that of ammonia has been established. The relation of the two processes may be the following, if Thompson's electron hypothesis be adopted.

In sodium chloride the sodium and chlorine are held together by the affinity each has for a negative electron.  $\text{Na}-\theta-\text{Cl}$ . On going into aqueous solution the atoms separate and chlorine having the greater affinity for the electron (+ 1.965 volts to - 2.54 volts for the sodium in normal solution) takes it away from the sodium. The sodium being thus left with an unsaturated affinity for a negative charge becomes a positive ion; the chlorine with a free negative charge becomes a negative ion. The free charges being on separate atoms and free to move the solution conducts the current. In the albumin molecule of amphoter reaction hydrogen ions are dissociated at one place; hydroxyl at another. A free positive charge and a free negative charge reside on the same molecule though on different atoms. The albumin molecule may, therefore, be unable to take part in the conduction of the current although ionized.



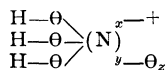
In the nitrogen atom as it exists in ammonia the opposite charges are on the same atom. The condition may be represented as follows where nitrogen is trivalent.



If N is the nitrogen atom it has three valencies satisfied by hydrogen. At  $x$  and  $y$ , two points on its surface, there is a positive charge not entirely compensated by the atom itself. This charge is compensated by the electron  $z$ . This electron may be regarded as holding together the two parts of the nitrogen atom at  $x$  and  $y$ , just as the electron held together the separate atoms

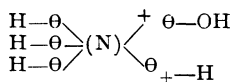
<sup>1</sup> Mathews, *Amer. Journal of Physiology*, 1904, X., p. 290.

of sodium and chlorine. In this case, I assume, the condition is that of Nef's polarized valencies. Particles in this condition he assumes to be inert so far as valencies  $x$  and  $y$  are concerned. Nef assumes that these polarized valencies open up and they open up more readily under some conditions than under others. For example, the polarized valencies of the carbon atom open up when the carbon is joined to nitrogen as in the isocyanides far more easily than they do when the carbon is joined to oxygen, as in carbon monoxide. The opening up of the valence is, I think, identical in character with the dissociation of a salt into its ions. The opening of these valencies constitutes a dissociation of valencies. It makes, of course, no difference theoretically whether those valencies are on the same atom or on different atoms. At any rate  $\text{NH}_3$  goes over into :



These are Nef's active particles. It is only when in this condition of dissociation that these valencies will combine. One of these valencies ( $x$ ) is positive; the other ( $y$ ) is negative. Such particles, although they are really in an ionic form, cannot conduct the current because they are positive and negative at the same time.

These particles combine as follows :



Exactly the same reasoning applies to all atoms, including bivalent carbon. It will be seen, therefore, that this explanation which is but a trifling addition to the fundamental idea of Nef of polarized valencies, would bring the respiratory reactions into the domain of electrical reactions. No doubt this explanation has occurred to others, and I give it only as a convenient picture. It bridges so well the gap between Nef's views of organic reactions and Ostwald's hypothesis that inorganic reactions are ionic that it may be useful.

It will be noticed also that upon this view residual valencies may be pictured as polarized valencies and in each case both pos-

itive and negative valencies are opened simultaneously. The number of residual valencies may be considerable since upon Thompson's hypothesis of the electronic constitution of matter the movement outward of any electron owing to the speed of rotation of the atom or a disturbance of its electrical equilibrium would open up such valencies. In fact, the whole atom would be made up of polarized valencies if we look at it in this way.

#### SUMMARY AND CONCLUSION.

The foregoing hypothesis has a close bearing on the spontaneous origin of living matter. As a result of chemical and histological work it is now clear that living matter is a mixture of various substances and is not a chemical compound ; there is no living compound. While this conclusion may not be admitted by all, it is, in my opinion, clearly established. There is no longer any doubt that the different phenomena of life are due to different constituents in this mixture. The histological, physiological, pharmacological and chemical evidence is unanimous on this point. The problem of the origin of life no longer appears, therefore, under its former guise, of how the foods are transformed into a living molecule or compound, but in its place we have instead, how are the foods transformed into the mixture of substances which is called living matter.

The question which we have to answer is this : is the transformation of the foods into living matter produced by the foods ; or is it produced by the living matter ? At first glance everyone would say that the transformation was caused by the living matter. This is the answer everyone has given hitherto and its truth appears to be self-evident. If we mix the foods by themselves they do not produce living matter. This answer has made it difficult to see how living matter originated on the earth. Preëxisting living matter was always needed to get living matter.

In the light of the foregoing discussion and the study of the transformations of the foods in protoplasm it appears highly probable that this answer is erroneous. Living matter does not cause the transformation of foods into living matter as we imagine ; instead the foods to-day spontaneously change themselves into living matter just as they did at the beginning. The change goes on very rapidly in living matter, but very slowly outside.

The cause of the formation of living matter is to be sought in the foods and not in the living matter.

As this conclusion has not so far as I know been hitherto perceived, the reasons for it may be briefly presented. They are in brief two: The examination of protoplasm has shown that it contains a great number of catalyzing agents or ferments. So many of these have been found in all cells and so clearly do protoplasmic reactions partake of this nature that the opinion is widely accepted that the chemical transformation of the foods in protoplasm into the substances constituting protoplasm is brought about by ferments. The work which has been done by the physical chemists and others upon ferments shows in the clearest manner that ferments are substances which do not cause reactions, they only accelerate reactions which will go on anyway in their absence, but which go on very slowly. Ferments therefore are accelerators of spontaneous reactions. Zymase does not cause the decomposition of the sugar molecule, it only accelerates its decomposition. The necessary result of this fundamental conception of the nature of ferment actions is this: the nature of the chemical transformations which the foods undergo in protoplasm is not altered or determined by the protoplasm. The nature of the transformation is determined by the foods; protoplasm by means of the ferments it contains only influences the *rate* of the transformation. This means as already pointed out that the foods must spontaneously transform themselves into the mixture called protoplasm, if given time enough. In protoplasm this transformation goes on very rapidly because some of the products of the reaction act as catalyzers to hasten the rate of this or that phase of the reaction.

In the second place a careful study of the transformations of the foods within and outside of protoplasm has failed to show a single instance in which the character of the transformation is different in two cases. This result is now so well understood in physiological chemistry that if we wish to discover what substances are formed out of any food or other substance during its passage through protoplasm, we subject the substance to decompositions, hydrolytic, oxidative, or reducing, outside the body, determine the substances formed and then look for these substances in the organism knowing that they will be formed there also.

In the third place a mass of evidence shows that substances outside the body simply dissolved in water, break up at a very slow rate, but into the same compounds in many instances as appear at a rapid rate in protoplasm.

These facts may be summarized in the general statement : Living matter does not determine the *character* of the transformation of the foods ; it only determines the *rate* of transformation.

This conclusion at once makes clear that living matter is to-day originating spontaneously from the foods just as it always has. The transformation goes on now very rapidly owing to catalyzers in protoplasm, whereas originally the transformation probably went on slowly until some of the products of the reaction were produced which acted as catalyzers for this or that phase. What we call living matter is of importance in the process only because it contains from the outset these end-product catalyzers, formed from the previous reaction. The whole process is, I conceive, as follows :

The carbon constituents of the foods spontaneously decompose. By this decomposition particles in a nascent state are formed. Upon Nef's hypothesis these would be particles with bivalent carbon. Whatever their nature these nascent particles either act on the water, oxidizing themselves to aldehydes or ketones and setting free hydrogen and in this manner causing protoplasmic respiration ; or they combine with each other to form the various constituents of protoplasm and thus cause growth. What they combine with depends on what substance is near when they become nascent. If it is ammonia amids, amino-acids and other nitrogen compounds are formed ; if another carbon compound, the carbon chains are built up and the complex substances which make up protoplasm. The whole process is due to a spontaneous dissociation of the food molecules and is not due to any vital energy. Some of the end-products of this spontaneous rearrangement act as ferments, that is, as accelerators of some phase of the reaction, or they may act as negative catalyzers delaying some phase. Examples of such processes are well known in chemical reactions. In exactly what manner they accelerate or delay the reaction is not certain.

The bearings of this conclusion upon many problems of biology, and particularly upon the problem of differentiation in



development is obvious. The substances produced from the foods depend on the foods and not on the protoplasm. The so-called organ-forming substances of the egg described by Whitman, Lillie, Conklin and others, determine necessarily the character of the protoplasm formed from them. There is but one other factor to be considered, *i. e.*, the presence of catalyzers which may accelerate different phases of a reaction. By this means a food substance, undergoing in many different cells the same course of transformation, will give rise in each to different proportions of substances, depending upon what stage of its transformation is accelerated. Thus, for example, a sugar undergoing one transformation into alcohol, lactic acid and carbon dioxide, or other substances may very readily give rise almost exclusively to lactic acid, if the proper phase is accelerated.

In this way, it is possible to see how the same foods in different protoplasms will form substances which are present in the different cells in widely different proportions. A specific instance will make this clear. Amino-acids spontaneously split off the amid group and form oxyacids. This occurs at a very slow rate and is a reversible change. In the liver of mammals there is a catalyzer which greatly accelerates this transformation. The result is that in this organ quantities of ammonia are produced and a non-nitrogenous residue. In cells lacking this ferment, this reaction goes on so slowly that there is no opportunity for the accumulation and farther decomposition and recombination of the products thus set free. Numerous other examples will occur to all physiological chemists.

In conclusion, I wish to point out that this conception is in many important particulars only an application to some of the problems of physiological chemistry of Nef's theory of the nature of organic chemical reactions. As will be seen from this paper, I believe that his hypothesis of the spontaneous decomposition of organic molecules with the formation of extremely reactive dissociation products throws a new light on the chemical transformations in protoplasm, and that many of those reactions become clear at once if it be assumed that the reactive particles have the properties of bivalent carbon. The importance of this theory for physiological chemistry is not yet sufficiently recognized.